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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/735,024	12/12/2000	Brian Seed	08100/003003	5494

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EXAMINER	
HUI, SAN MING R	

ART UNIT	PAPER NUMBER
1617	7

DATE MAILED: 02/26/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/735,024	SEED ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 55-71 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 55-71 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This is a continuation of US Application Serial No. 09/198,874 which is a continuation of US application Serial No. 08/680,684.

Claim Objections

Claims 58 and 66 are objected to because of the following informalities: the expression "combination comprises aspirin" is confusing because aspirin is not considered by one of ordinary skill in the art as cholesterol synthesis or transfer inhibitor. Appropriate correction is required. Adding the word "further" before the word "comprises" would be favorably considered by the examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 55-60, 62-63, 65-68, and 70-71 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for cholesterol synthesis or transfer inhibitor disclosed in page 7 in the specification, lines 3-12, does not reasonably provide enablement for other cholesterol synthesis or transfer inhibitors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

Applicant fails to set forth the criteria that defines neither a "cholesterol synthesis inhibitor" or "cholesterol transfer inhibitor". Given that there is no common core structural, physical or chemical properties of the cholesterol synthesis inhibitors or cholesterol transfer inhibitors have been provided, the skilled artisan would be required to conduct undue experimentation in order to select compounds that will be useful in the practice of the instant invention.

Additionally, Applicant fails to provide information allowing the skilled artisan to ascertain these compounds without undue experimentation. In the instant case, only a

limited number of "cholesterol synthesis inhibitor" or "cholesterol transfer inhibitor" examples are set forth, thereby failing to provide sufficient working examples. It is noted that these examples are neither exhaustive, nor define the class of compounds required. The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. The instant claims read on all "cholesterol synthesis inhibitor" or "cholesterol transfer inhibitor(s)", necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. Applicants fail to provide information sufficient to practice the claimed invention, absent undue experimentation.

Furthermore, Claims 60-61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for fish oil does not reasonably provide enablement for other marine lipid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There is no adequate direction provided by the applicant as to how to select other marine lipids which would be suitable for the use in the practice of the instant invention.

The instant specification only provide a limiting number of working examples to point out how other marine lipids other than fish oils may be used successfully in the claimed stenosis-reducing method. It is noted that these examples are neither exhaustive, nor define the class of compounds required. The pharmaceutical art is

unpredictable, requiring each embodiment to be individually assessed for physiological activity.

Moreover, it is known in the art that different active compounds that have structural differences may have different potency and activity. Therefore, different marine lipids such as those having different alkyl chain length, either branched or non-branched; with or without amino groups, bridged and/or cyclic moieties, esters etc., would result in correspondingly different activity for the resulting marine lipids compounds. The instant claims read on **all** "marine lipids", necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. Please note that there is no common core structural, physical or chemical properties of marine lipids have been provided. Due to this unpredictability, it would prevent the skilled artisan from selecting a marine lipid to retain the function of the instant stenosis-reducing method, as currently claimed, without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 55-71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The expression "compound comprising ..." in claim 55, line 3 renders the claims indefinite because it is unclear the meaning of compound encompassed in the claims.

Do the claims intend to encompass one compound or one composition comprising more than one compound?

The expression "cholesterol ... transfer inhibitor" in claim 55 renders the claims indefinite as to the compounds encompassed thereby.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 55-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sassen et al. (Cardiovasc. Drugs ther., 1994; 8(2):179-191), Vane et al. (Circulation, 1991; 84(6):2588-2590), Lee et al. (Am. J. Cardiol., 1994; 73(15):1037-1040), Watts et al. (Lancet, 1992; 339(8793):563-569), and Demopulos et al. (US Patent 5,800,385).

Sassen et al. teaches fish oil, which contains eicosapentaeneoic acid and docosahexaeneoic acid, can cause atherosclerotic lesion regression and prevent

progression of atherosclerosis (See particularly page 180, col. 1, first paragraph; and col. 2, last paragraph; also 186, col. 2 - 187, col. 1). Sassen et al. also teaches the dosages of eicosapentaeneoic acid and docosahexaeneoic acid used in the method of causing regression of atherosclerotic lesions and preventing progression of atherosclerosis are 100-700 mg/kg/day respectively (See page 183, Table 3 and page 184, Table 4). For an average 70kg adult, the dosage will be 7 – 49 g/day.

Vane et al. teaches that 50 – 1,300mg/day of Aspirin plus fish oil are useful in vasodilatation and platelet inhibition (See page 2588, col. 1, last, paragraph and page 2589, col. 1, last paragraph).

Lee et al. teaches that 10mg of pravastatin and 1500mg of niacin daily are useful in prevention of restenosis (See the abstract).

Watts et al. teaches cholestyramine with lipid-lowering diet are useful in regression of atheroslcerosis by 66% (See particularly abstract and page 568, col. 1, second paragraph). Watts et al. also teaches that cholestyramine with lipid-lowering diet increasing coronary artery diameter as the LDL cholesterol concentration decreases (See page 568, col. 1, second paragraph; also col. 2, first paragraph). Watt et al. also teaches that patients taking cholestyramine with lipid-lowering diet can lowered the LDL concentration to about 1.71 mmol/l or 65.7mg/dl (1.71 mmol/l x 200mg/dl / 5.2mmol/l = 65.7mg/dl) (See page 567, col. 1, Fig. 1).

Demopulos et al. teaches buspirone is useful in an anti-restenosis method (See particularly the abstract, col. 13, line 9-10 and claims 1).

The references do not expressly teach the agents are useful together in a method of reducing coronary artery stenosis. The references do not expressly teach the LDL concentration to be less than 55 mg/dl. The references do not expressly teach the dosage of aspirin to be greater than 80 mg/day. The references do not expressly teach the dosage of buspirone to be between 10-80 mg/day.

It would have been obvious to one skill in the art when the invention was made to employ the agents herein together with lower-lipid diet in a method of reducing coronary artery stenosis (narrowing). It would have been obvious to one skill in the art when the invention was made to employ greater than 80 mg/day of aspirin and 10-80 mg/day of buspirone in the method of reducing coronary artery stenosis. It would have been obvious to one skill in the art when the invention was made to lower the LDL concentration in the patient to below 55 mg/dl.

One of ordinary skill in the art would have motivated to employ the agents herein together with lower-lipid diet in a method of reducing coronary artery stenosis (narrowing) because all the agents herein are known to prevent or treat restenosis or cause vasodilatation. Therefore, combining two or more agents which are known to be useful to prevent or treat restenosis or cause vasodilatation individually into a method useful for reducing coronary artery stenosis or coronary artery narrowing is *prima facie* obvious.

One of ordinary skill in the art would have motivated to employ greater than 80 mg/day of aspirin and 10-80 mg/day of buspirone in the method of reducing coronary

artery stenosis because the optimization of result effect parameters (e.g., dosage range) is obvious as being within the skill of the artisan.

One of ordinary skill in the art would have motivated to lower the LDL concentration to below 55 mg/dl because LDL cholesterol concentration is inversely proportional to the regression of coronary atherosclerosis (coronary artery narrowing) i.e., the lower the LDL concentration, the greater the regression of coronary atherosclerosis. Therefore, lowering the LDL concentration would have been reasonably to be useful in the method of reducing coronary artery stenosis.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Minna Moezie, J.D., can be reached on (703) 308-4612. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui
February 24, 2002

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